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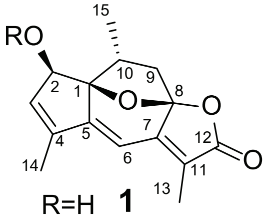
The studies on structures and absolute stereochemistry of secondary metabolites using various modern approaches

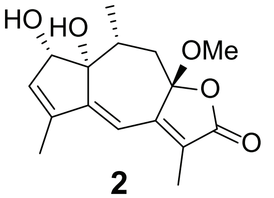
We discuss the latest results of structure elucidation of new natural products that were recently isolated. A complex approach was used to determine the configurations of the asymmetric centers in natural products, based on the chemical transformations, and the calculation of stable conformations of the rings along with a comparison of experimental ECD, NMR spectra, and specific optical rotations with those theoretically calculated by quantum-chemical methods.

Key words: natural product, absolute stereochemistry, NMR, ECD, quantum chemical modeling

Determination of the absolute handedness, known as absolute configuration of chiral molecules, is an important step in any field of organic chemistry, especially for the structure elucidation of new natural products.



R=H **1**
R=(*R*)MTPA **1r**
R=(*S*)MTPA **1s**



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Two new unusual guaiane sesquiterpenoids were isolated from the gorgonian *Menella woodin*. Their structures and relative configurations were determined by the extensive spectroscopic analysis. However, we were able to use a complex approach to determine the absolute configurations of the asymmetric centers of the compounds **1** and **2**. With the application of the Mosher's method, the 2*R* configuration was determined. Then, the diverse array of computational techniques, including calculation of the coupling constants, ^{13}C NMR chemical shifts, optical rotation and ECD allow to determine the absolute configurations of isolated compounds.

Quantum-chemical calculations, using B3LYP non-local exchange-correlation functional [1, 6] along with the 6-311G(d,p) basis set and polarisation-continuum model (PCM) [5],

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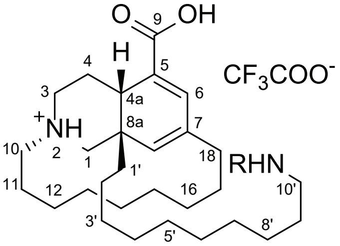
implemented using the Gaussian 03W package of programs [3],were used for further studies on the stereochemistry of **1** and to solve similar problems of **2**. In particular, the time-dependent density functional (TD-DFT) theory was used for the calculations of ECD spectra. The GIAO variant of theory was used for calculating NMR isotropic shielding constants.

The comparison of statistically averaged theoretical ECD spectra of 1*S*,2*R*,8*S*,10*R* (**1a),** 1*S*,2*R*,8*S*,10*S* (**1b)** (all of them could demonstrate similar NOE correlations) with experimental ECD showed a good qualitative agreement between the experimental spectrum and calculated ECD of **1a** and **1b**, confirming the 1*S*,2*R*,8*S* absolute stereochemistry in **1**, corresponding with NOE data and the results of Mosher's method application. However, the theoretical ECD spectra for **1a** and **1b** were quite similar doing impossible the C10 configuration determination. Thus, the limited capability of ECD spectroscopy, NMR data, and results of Mosher's method to complete the structure elucidation of **1** without additional information was brought out.

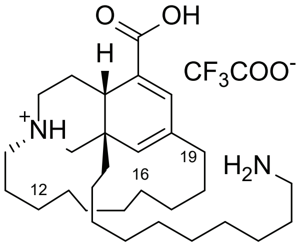
The comparison of theoretical and experimental chemical shifts δ_C of C9, C10 and δ_H of H9α, H9β as well as the comparison of calculated coupling constants $^2J_{H9\alpha,H9\beta}$, $^3J_{H9\alpha,H10}$ and $^3J_{H9\beta,H10}$ with corresponding experimental values allowed us to resolve this problem and establish the absolute stereochemistry of **1** as 1*S*,2*R*,8*S*,10*R*. Calculated spin-spin coupling constants of **1a** were in agreement with the corresponding experimental values. All of this data assigned the signals of H9a at δ_H 1.68 as α, H9b at δ_H 2.68 as β and Me15 as α, respectively. In conclusion the specific optical rotation of 1*S*,2*R*,8*S*,10*R*-**1** was calculated. The positive sign and statistically averaged $[\alpha]_{D,calc}$ = +514 corresponded to the experimental value of $[\alpha]_{D,exp}$ = +217. Thus, the structure of **1** was established on the basis of all discussed data as (1*S*,2*R*,8*S*,10*R*)-1,8-epoxy-2-hydroxy-guaian-3,5,7-trien-12,8-olide.

The strong negative specific optical rotation of **2** ($[\alpha]^{26}_{D}$ = 206) as well as antipodal ECD spectrum in comparison with **1** assumed a significant difference in the stereochemistry of the compounds. The relative and absolute stereochemistry in **2** was determined on the basis of a comparison of ECD and NMR spectra, calculated for the energetically most preferable conformations of different stereoisomers of **2** with those obtained for **2** experimentally. Specifically, the comparison of experimental and calculated NMR data showed that only the 1*R*,*2*S*,*8*S*,*10*R** structure with an equatorial position of Me15 correctly reproduces all features of the recorded NMR spectra. Attempts to assign the recorded NMR data to any other stereoisomer showed significant differences between observed and calculated constants and $\Delta\delta_{C(10-9)}$ values. The calculated ECD for the (1*R,*2*S,*8*S,*10*R*) stereoisomer of **2** showed a similar CD curve with the experimental ECD spectrum. Finely, the specific optical rotation of (1*R,*2*S,*8*S,*10*R*)-**2** was calculated. The negative sign and large value of statistically averaged $[\alpha]_{D,calc}$ = -594 was in accordance with the experimental value $[\alpha]_{D,exp}$ = -206 and proved the 1*R,*2*S,*8*S,*10*R* stereochemistry of **2** [2].

The quantum chemical modeling was also introduced for the absolute configurations elucidation in the lissodendoric acids A (**3**) and B (**4**), isolated from the sponge *Lissodendoryx florida.* The structures of the first representatives of a new group of manzamine-related alkaloids with previously unknown skeleton systems were determined by the extensive spectroscopic analysis together with chemical transformations. The comparison of statistically averaged theoretical



R=H **3**
R=Ac **3a**



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ECD spectra of both enantiomers of acetylated lissodendoric acid A (**3a**) with experimental ECD showed a good agreement between the curves, confirming the (4a*S*,8a*S*) absolute stereochemistry, corresponding with NOE data and the possible biogenetic pathway [4].

The achieved results in the field of structural research of new natural products demonstrate the advantages of an integrated approach, including methods of quantum chemical modeling, directed chemical transformations together with consideration of biosynthesis pathway.

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